Use of the Adaptive LASSO Method to Identify PM$_{2.5}$ Components Associated with Blood Pressure in Elderly Men: The Veterans Affairs Normative Aging Study

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National Institute of
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Lingzhen Dai,[1] Petros Koutrakis,[1] Brent A. Coull,[2] David Sparrow,[3] Pantel S. Vokonas,[3] and Joel D. Schwartz[1]

[1]Department of Environmental Health, and [2]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA; [3]Veterans Affairs Normative Aging Study, Veterans Affairs Boston Healthcare System, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts, USA

Address corrrespondence to Lingzhen Dai, Department of Environmental Health, Harvard T.H. Chan School of Public Health, Landmark Center 4th floor, 401 Park Drive, Boston, MA 02215 USA. E-mail: ldai@mail.harvard.edu

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Abstract

Background: $PM_{2.5}$ has been associated with adverse cardiovascular outcomes, but it is unclear whether specific $PM_{2.5}$ components, particularly metals, may be responsible for cardiovascular effects.

Objectives: To determine which $PM_{2.5}$ components are associated with blood pressure in a longitudinal cohort.

Methods: We fit linear mixed-effects models with the adaptive LASSO penalty to longitudinal data from 718 elderly men in the Veterans Affairs Normative Aging Study, 1999-2010. We controlled for $PM_{2.5}$ mass, age, body mass index, use of antihypertensive medication (ACE inhibitors, non-ophthalmic beta blockers, calcium channel blockers, diuretics, and angiotensin receptor antagonists), smoking status, alcohol intake, years of education, temperature, and season as fixed effects in the models, and additionally applied the adaptive LASSO method to select $PM_{2.5}$ components associated with blood pressure. Final models were identified by the Bayesian Information Criterion (BIC).

Results: For systolic blood pressure (SBP), Ni and Na were selected by the adaptive LASSO, whereas only Ni was selected for diastolic blood pressure (DBP). An IQR increase (2.5 ng/m^3) in 7-day moving average Ni was associated with 2.48 (95% CI: 1.45, 3.50) mm Hg increase in SBP and 2.22 (95% CI: 1.69, 2.75) mm Hg increase in DBP, respectively. Associations were comparable when the analysis was restricted to study visits with $PM_{2.5}$ below the 75th percentile of the distribution (12 µg/m^3).

Conclusions: Our study suggested exposure to ambient Ni was associated with increased blood pressure independent of $PM_{2.5}$ mass in our study population of elderly men. Further research is needed to confirm our findings, assess generalizability to other populations, and identify potential mechanisms for Ni effects.

Introduction

Studies have shown that exposure to fine particulate matter ($PM_{2.5}$, particles ≤ 2.5 µm in aerodynamic diameter) is associated with cardiovascular morbidity and mortality (Franklin et al. 2008; Laden et al. 2006; Miller et al. 2007; Zanobetti et al. 2009). $PM_{2.5}$ consists of various components, including organic and elemental carbon, metals, and ions. Some national studies have evaluated whether $PM_{2.5}$ components may have differential effects on cardiovascular health (Dai et al. 2014; Peng et al. 2009), but it still is not clear whether specific components may be responsible for $PM_{2.5}$-related cardiovascular effects.

Increased blood pressure is a major risk factor for cardiovascular events. Several studies have investigated the relationship between PM and blood pressure. However, the results have varied, possibly because of differences in the particle composition (Baccarelli et al. 2011; Choi et al. 2007; Chuang et al. 2010; Dvonch et al. 2009; Harrabi et al. 2006; Hoffmann et al. 2012; Ibald-Mulli et al. 2004; McCracken et al. 2007; Schwartz et al. 2012; Wilker et al. 2009; Wilker et al. 2010).

Inhaled PM-associated metals may be able to translocate from lung into systemic circulation and induce adverse effects on cardiovascular system (Wallenborn et al. 2007). There is growing evidence supporting adverse effects of ambient metals on cardiovascular health. For example, Fe, K, Ti, and Zn in fine particles were positively associated with cardiovascular mortality in a California study (Ostro et al. 2007). A multiple-community study reported that Ni and Na^+ modified associations of $PM_{2.5}$ on hospital admissions due to cardiovascular diseases (Zanobetti et al. 2009). There were also numerous animal studies that reported cardiovascular toxicity of PM metal components Zn, Ni, and V (Campen et al. 2001; Chuang et al. 2013; Kodavanti et al. 2008; Lippmann et al. 2006). In terms of sources, PM-associated metals usually come from road

dust (e.g., Ca, Al, Fe, and Ti), oil combustion (e.g., Ni and V), traffic emission (e.g., Zn and Cu), wood burning (e.g., K), and sea salt (e.g., Na).

In this study, we examined the association between blood pressure and 11 $PM_{2.5}$ components, including 8 metals (Fe, K, Al, Ni, V, Cu, Zn, and Na) and 3 non-metals (S, Si, and Se), with longitudinal data from the Veterans Affairs Normative Aging Study.

Methods

Study population

The Normative Aging Study (NAS) was established in 1963 by the Department of Veterans Affairs (Bell et al. 1972). Briefly, it is an ongoing longitudinal study of aging, which enrolled 2,280 community-dwelling, healthy men living in the Greater Boston area. Participants were free of known chronic medical conditions at enrollment and have undergone examinations every 3 to 5 years, including physical examinations and questionnaires. All participants provided written informed consent. The study was reviewed and approved by the Institutional Review Boards of all participating institutions.

After excluding participants with incomplete information for any of the covariates of interest, those who died, or those who moved out of New England, a total of 718 participants with 1,567 observations had examinations between March 1999 and October 2010. Of the 718 participants, 235 (33%) had one visit, 195 (27%) had two visits, and 288 (40%) had three or more visits.

Blood pressure measurements

During a clinical visit, a physician uses a standard mercury sphygmomanometer with a 14-cm cuff to measure blood pressure for the subject while he is sitting, including systolic blood

pressure (SBP) and fifth-phase diastolic blood pressure (DBP) in each arm to the nearest 2 mm

Hg. We used the means of the left and right arm measurements as a subject's SBP and DBP.

Environmental data

Daily ambient $PM_{2.5}$ and its components were measured at the stationary ambient monitoring site

at the Harvard University Countway Library (Kang et al. 2010), using the Tapered Element

Oscillating Microbalance (TEOM 1400a, Rupprecht & Patashnick Co.) and the Energy

Dispersive X-ray Fluorescence Spectrometer (Epsilon 5, PANalytical), respectively. The

monitoring site is 1 km from the clinical examination site.

We obtained daily temperature data from Boston Logan airport weather station.

Statistical analysis

We used 7-day moving average concentrations for $PM_{2.5}$ and the following 11 components, K, S,

Se, Al, Si, Fe, Ni, V, Cu, Zn, and Na, since previous studies have suggested that PM averaging

over that time period is strongly associated with blood pressure (Mordukhovich et al. 2009;

Wilker et al. 2010; Zanobetti et al. 2004). We focused on these components because their

concentration levels are mostly above the method detection limits and they are representative of

different PM sources (Hopke et al. 2006). In the analysis, we controlled for continuous variables

age, body mass index [BMI, computed as weight (in kilograms) divided by height (in square

meters)], years of education, linear and quadratic terms of mean temperature of visit day, and

categorical variables use of each individual types of antihypertensive medication (ACE

inhibitors, non-ophthalmic beta blockers, calcium channel blockers, diuretics, and angiotensin

receptor antagonists), smoking status (3 categories: never, former, current smoker), alcohol

intake (whether the participant takes two or more drinks per day, yes or no), and season (4

categories; defined as spring: March-May, summer: June-August, fall: September-November,

winter: December-February) regardless of statistical significance as these variables have been

shown to predict cardiovascular health (Mordukhovich et al. 2009; Schwartz et al. 2012). In

addition, we adjusted for potential confounding of associations with $PM_{2.5}$ components by $PM_{2.5}$

mass (Mostofsky et al. 2012). All variables were measured at each visit. We forced these

covariates to be included in the models and estimated their fixed effects with no penalization.

Selecting important predictors from a large list of correlated predictors is difficult, and most

methods are empirical. Approaches such as stepwise methods ignore stochastic errors inherited

in the stages of variable selection (Fan and Li 2001) and can yield falsely narrow confidence

intervals (Harrell 2001). To improve on this, we applied the adaptive LASSO method to select

important component(s) that may be associated with blood pressure from those 11 $PM_{2.5}$

components. Briefly, the LASSO (Least Absolute Shrinkage and Selection Operator) is a

regression shrinkage and selection approach that applies an ℓ_1 penalty to the component

regression coefficients. This penalty essentially minimizes the sum of squared errors subject to

the sum of the absolute values of the coefficients being less than a given value (Tibshirani 1996).

The adaptive LASSO is a later version of the LASSO, which uses weights for penalizing

different coefficients in the ℓ_1 penalty and enjoys the oracle properties, which means, given that

the true model depends only on a subset of the predictors, this selection procedure is able to

identify the right subset model and satisfies asymptotic normality (Fan and Li 2001; Zou 2006).

Since subjects had repeated measures, we fit linear mixed-effects models with random subject-

specific intercepts to capture the correlation among different measurements within the same

subject, as follows:

$$Y_i = X_i\alpha + Z_i\beta + \mu_i + \varepsilon_i \,, \tag{1}$$

where, Y_i is the blood pressure level (SBP or DBP) of subject i, $X_i = (X_{i1}, \ldots, X_{iP})^T$ is a vector of PM$_{2.5}$ mass and other covariates, $Z_i = (Z_{1i}, \ldots, Z_{iM})^T$ is a vector of PM$_{2.5}$ components, μ_i is the random intercept. Hence, α indicates the fixed effects of PM$_{2.5}$ mass and other covariates X_i, and β is the penalized effects of PM$_{2.5}$ components Z_i that are given by the adaptive LASSO.

First, we used the ordinary linear mixed-effects (LME) model to obtain non-zero coefficients (β_{lme}) for each component, and computed the adaptive weight as its inverse ($w = 1/\beta_{lme}$). Heuristically, this allows us to give less weight in the penalty to variables whose standardized regression coefficients are large, since they are more likely to be predictors. When using the adaptive LASSO, we assign a non-negative penalty parameter, λ, to determine how strongly we penalize, or restrict, the magnitude of the PM$_{2.5}$ components regression coefficients. When λ is equal to 0, there is no shrinkage and the model is just the ordinary mixed-effects regression of the fixed covariates and all components; when it is large enough, there is maximum shrinkage, yielding a model that includes fixed covariates only and all component coefficients equal to 0; when λ takes some value in between, some coefficients are 0, and the model is a penalized model. Components with non-zero coefficients are "selected" by the adaptive LASSO. In this way, the method chooses PM$_{2.5}$ components that may be associated with the outcomes. We ran the models across that range of λ's, i.e., from no shrinkage to maximum shrinkage, and chose the λ having the smallest Bayesian Information Criterion (BIC) (Schwarz 1978). Last, we used the mixed-effects model with fixed covariates and selected components only to obtain the estimated effects and corresponding 95% confidence intervals.

In a sensitivity analysis, we omitted study visits with PM$_{2.5}$ below the 75th percentile of the distribution (12 $\mu g/m^3$).

Data cleaning was performed with SAS 9.3 (SAS Institute Inc.), and data analysis was performed

with R 3.0.1 (http://www.r-project.org/).

Results

Table 1 summarizes the characteristics of study population. Subjects in this study were elderly

men, with a mean age of 73 years (SD = 7 years) at the first visit. Average SBP and DBP at the

first visit were 132 mm Hg (SD = 17 mm Hg) and 76 mm Hg (SD = 10 mm Hg), respectively.

$PM_{2.5}$ and component concentrations are shown in Table 2. 7-day moving average $PM_{2.5}$ across

all study visits had a mean of 10 µg/m^3 (SD = 3.7 µg/m^3), with an IQR of 4.3 µg/m^3. S accounted

for the largest proportion of the total $PM_{2.5}$ concentration (10.4%), followed by Na (1.9%). The

average concentration of Ni was 3.1 ng/m^3 (SD = 2.5 ng/m^3), and it only accounted for 0.03% of

the mass concentration.

Figure 1 shows the relationship between BIC, a criterion for model selection and λ, the adaptive

LASSO penalty parameter. For SBP models, the model with the smallest BIC had λ = 4 and Ni

and Na as the only two among the eleven $PM_{2.5}$ components (i.e., K, S, Se, Al, Si, Fe, Ni, V, Cu,

Zn, and Na) with non-zero coefficients, whereas all component coefficients were zero when λ =

9. For DBP models, the model with the smallest BIC had λ = 13 and Ni as the only component

with a non-zero coefficient, whereas all component coefficients were zero when λ = 30.

In models fitted using only the selected components, we found an IQR increase (2.5 ng/m^3) in 7-

day moving average Ni was associated with a 2.48 (95% CI: 1.45, 3.50) mm Hg increase in SBP

and 2.22 (95% CI: 1.69, 2.75) mm Hg increase in DBP, respectively. To compare with other

studies, we also estimated the effects of $PM_{2.5}$ mass: every 10 µg/m^3 increase in 7-day moving

average $PM_{2.5}$ was associated with 1.36 (95% CI: -1.67, 4.39) mm Hg increase in SBP and 0.61

(95% CI: -0.85, 2.07) mm Hg increase in DBP, respectively.

LASSO coefficient paths for SBP and DBP are shown in Figure 2. Each component coefficient is

expressed as the change in mean SBP or DBP per 1-$\mu g/m^3$ increase in the 7-day moving average

concentration of the $PM_{2.5}$ component. Each curve indicates the rate at which the component

coefficient shrinks towards zero as λ increases. When $\lambda = 0$, all components have non-zero

coefficients.

Table 3 shows the comparison of results from the main analysis and the sensitivity analysis that

was restricted to data from study visits with $PM_{2.5}$ concentrations below the 75th percentile of the

distribution (12 $\mu g/m^3$). We found that the estimated coefficients of Ni for both SBP and DBP in

the sensitivity analysis were comparable to those in the main analysis, and their statistical

significance remained. That is, Ni was associated with SBP and DBP even when overall $PM_{2.5}$

concentrations were restricted to < 12 $\mu g/m^3$.

Discussion

In this study, we used the adaptive LASSO shrinkage method to choose $PM_{2.5}$ components that

might be related to blood pressure in a cohort of elderly men. We found that 7-day moving

average Ni and Na were associated with SBP, and 7-day moving average Ni concentration was

also associated with DBP. This association persisted when restricted to data from study visits

with $PM_{2.5}$ concentrations below 12 $\mu g/m^3$.

Ni in ambient air is considered a marker of oil combustion; other sources of Ni include coal

combustion, nickel metal refining, sewage sludge incineration, and manufacturing facilities.

(EPA 2000). There have been a number of toxicological studies that examined the effects of

ambient Ni on cardiovascular health. In a mouse model of atherosclerosis, mice had acute

changes in heart rate and heart rate variability when exposed to concentrated fine PM (average

concentration of Ni was 43 ng/m^3 and there were Ni peaks at ~ 175 ng/m^3) (Lippmann et al.

2006). Another animal study showed that Ni inhalation caused a decrease of 75 bpm in maximal

heart rate at the concentration of 1.3 mg/m^3 and a decrease of 100 bpm at 2.1 mg/m^3 in rats

(Campen et al. 2001). Moreover, Ni was reported to induce increases in pulmonary protein

leakage and perivascular and peribronchiolar inflammation in both normotensive and

spontaneously hypertensive rats that were intratracheal instilled with 1.5 µmol/kg of

NiSO$_4$•6H$_2$O in saline (Kodavanti et al. 2001). A similar study found alterations in heart rate

variability (HRV) related to PM exposure were Ni-dependent in spontaneously hypertensive rats

after adjusted for HRV responses in control rats (Chuang et al. 2013).

Several epidemiological studies have provided evidence of cardiovascular effects of Ni. A

national study conducted in 106 U.S. counties reported that associations between PM$_{2.5}$

concentrations and cardiovascular and respiratory hospitalizations were stronger when Ni was

high (Bell et al. 2009). Zanobetti et al. (2009) examined associations of PM$_{2.5}$ with emergency

hospital admissions in 26 U.S. communities and found that Ni significantly modified the

association between PM$_{2.5}$ mass and hospital admissions for cardiac diseases and myocardial

infarctions. A recent study found a significant association between ischemic heart diseases

mortality and Ni based on data from the American Cancer Society (Lippmann et al. 2013). On

the other hand, Zhou and co-authors (2011) failed to find cumulative effects from lag 0 to lag 2

of Ni in Detroit or Seattle. A more recent nationwide study that included 75 U.S. cities did not

observe any effect modification of Ni in the PM$_{2.5}$-mortality association (Dai et al. 2014).

There are several possible reasons for the differences in these epidemiological studies. First, Ni concentrations are usually lower than the method detection limits, which makes it difficult to determine whether associations are present (Burnett et al. 2000). New York counties had particularly high levels of Ni (a mean of 19.0 ng/m³ Ni in New York fine PM vs. a mean of 1.9 ng/m³ Ni in national fine PM) due to combustion of residual oil-fired power plants and ocean-going ships (Lippmann et al. 2006). In a reanalysis of the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) data, Dominici et al. (2007) found evidence of effect modification by Ni, which was consistent with Lippmann et al. (2006); however, the effect modification of Ni on PM-mortality association was much weaker and no longer statistically significant when New York counties were excluded from the analysis. In the two studies that did not find significant associations of Ni, Ni had a relatively low level. For example, the national mean concentration of Ni was 2.5 ng/m³ in Dai et al. (2014). Given the substantial differences in Ni concentrations, it is conceivable that studies conducted in other places or nationally may not be able to observe the health effects of Ni as the New York studies did. In our study, Ni had an average concentration of 3.1 ng/m³, which was higher than the national mean but still much lower than New York levels (Dominici et al. 2007; Lippmann et al. 2006). Furthermore, it is possible that Ni interacts with other PM components to pose an increased risk to health. Campen et al. (2001) reported evidence of a synergistic interaction between Ni and V, both of which are markers of PM from oil combustion. Hence, the heterogeneous composition of PM in different locations might lead to different estimated effects of Ni.

Na also was selected, in addition to Ni, when the adaptive LASSO method was applied to identify PM$_{2.5}$ components associated with SBP. There is limited literature on the effects of

ambient Na on cardiovascular health. Zanobetti et al. (2009) documented that Na^+ modified the relationship between $PM_{2.5}$ and emergency hospital admissions for cardiac diseases.

In the study, 7-day moving average $PM_{2.5}$ concentration ranged from 3.2 to 34.3 $\mu g/m^3$, while daily $PM_{2.5}$ was in the range of 1.2 ~ 44.8 $\mu g/m^3$ with a 99th percentile of 34 $\mu g/m^3$. Hence, we identified associations in a study population that was usually exposed to $PM_{2.5}$ concentrations below the current EPA daily ambient standard 35 $\mu g/m^3$ (EPA 2012). Associations with Ni were similar when we excluded observations with 7-day moving average PM concentration ≥ 12 $\mu g/m^3$. Our findings may suggest stricter air quality standards.

To date, many studies have investigated the biological mechanisms of the adverse effects of inhalation exposures to PM on cardiovascular diseases. Brook et al. (2010) summarized there are three potential pathways: 1) inducing pulmonary oxidative stress and inflammation via the release of proinflammatory mediators or vasculoactive molecules; 2) interacting with lung receptors or nerves to perturb systemic autonomic nervous system balance or heart rhythm; 3) PM or PM components being transmitting into the systemic circulation. Metals are typical PM components. It has been documented that metals can enhance lung inflammation and injury (Ghio and Devlin 2001; Schaumann et al. 2004), which may be attributed to the metal-catalyzed oxygen stress via non-nitric oxide pathways (Dye et al. 1997). Nevertheless, mechanisms of cardiovascular effects of Ni have not been fully established. Previous studies have shown that metals in particles (e.g., Ni, V) could induce the activation of transcription factor NF-κB (a family of proteins that regulates DNA transcription in cellular responses such as immune, inflammatory response, and apoptosis), cell apoptosis and cell cycle regulation (Chen and Shi 2002; Goebeler et al. 1995; Quay et al. 1998). Although the clinical relevance is unclear, our

finding that an IQR increase in Ni was associated with a 2.48/2.22 mm Hg increase in blood pressure may imply elevated risks of cardiovascular outcomes induced by Ni.

The major strengths in the study were highlighted as follows. 1) We used a novel approach, the adaptive LASSO, to investigate the relationship between $PM_{2.5}$ components and health outcomes. This method has advantages over conventional approaches. Typically, researchers examined effects of components by including all components in models or by using conventional selection procedures, such as stepwise selection. Linear regression with all components included may fail to detect any association as the collinearity among components reduce power, while conventional selection methods make no guarantee to select the right variables asymptotically. 2) To our knowledge, this is the first longitudinal cohort study that examined the effects of PM-related metals on blood pressure. The study population was geographically stable, well described and followed up since the enrollment in 1963. 3) We had daily concentrations of PM metals for more than 10 years. In previous studies, especially large national/multi-city studies, researchers usually used data from EPA Air Quality System that was sampling PM components every 3rd or 6th day (Dai et al. 2014; Krall et al. 2013; Zanobetti et al. 2009), and hence had to face the challenge in lack of data.

On the other hand, there are several limitations in the study. Due to the use of stationary measures of $PM_{2.5}$ components, we were unable to capture the personal exposures of our subjects. Another limitation of our study is the potential measurement errors in blood pressure since blood pressure was measured only once at each study visit. Last, since the study population was limited to elderly men, most of whom were Caucasian, our findings cannot be directly generalized to women, younger men, or more diverse populations of elderly men. Subjects voluntarily continue to participate in the ongoing NAS study, so there may be volunteer bias if

healthier people are more likely to participate. Also, there would be survivor bias if people who

stay in the study are healthier than other people.

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Table 1. Characteristics of subjects in the study

Variable	First visit (n=718)	All visits (n=1,567)
Mean ± SD		
SBP (mm Hg)	131.6 ± 16.7	128.1 ± 17.6
DBP (mm Hg)	75.9 ± 9.9	71.9 ± 10.3
Age (years)	72.8 ± 6.8	74.7 ± 6.8
BMI (kg/m^2)	28.2 ± 4.0	28.0 ± 4.1
Education (years)	14.6 ± 2.8	14.6 ± 2.8
Number (%)		
Use of ACE inhibitors	197 (27%)	540 (34%)
Use of non-ophthalmic beta blockers	213 (30%)	554 (35%)
Use of calcium channel blockers	104 (14%)	265 (17%)
Use of diuretics	150 (21%)	381 (24%)
Use of angiotensin receptor antagonists	36 (5%)	124 (8%)
Current smokers	28 (4%)	47 (3%)
Former smokers	488 (68%)	1049 (67%)
Two or more drinks per day	143 (20%)	299 (19%)

Table 2. Mean $PM_{2.5}$ mass and component concentrations across all study visits

Pollutant	Mean ± SD	IQR	Proportion of $PM_{2.5}$ (%)
$PM_{2.5}$ (µg/m^3)	10.0 ± 3.7	4.3	
Components (ng/m^3)			
Fe	68.1 ± 24.2	21.5	0.7
K	39.2 ± 24.6	16.9	0.4
S	1039.1 ± 513.2	554.1	10.4
Al	51.8 ± 27.8	21.1	0.5
Si	76.7 ± 51.1	38.4	0.8
Ni	3.1 ± 2.5	2.5	0.03
V	3.5 ± 2.3	2.6	0.04
Cu	3.5 ± 1.2	1.5	0.04
Zn	11.4 ± 6.0	5.8	0.1
Se	0.2 ± 0.3	0.3	0.002
Na	190.7 ± 72.4	92.8	1.9

Table 3. Comparison of estimated coefficients of Ni in the main analysis and in the sensitivity analysis where study visits with 7-day moving average $PM_{2.5} \geq 12$ μg/m^3 were excluded

Analysis (No. of visits)	SBP		DBP	
	Coefficient	*p*-value	Coefficient	*p*-value
Main analysis (N = 1,567)	0.989	< 0.001	0.888	< 0.001
Sensitivity analysis (N = 1,201)	1.149	< 0.001	1.104	< 0.001

Figure Legends

Figure 1. The relationship between BIC, a criterion for model selection and λ, the adaptive LASSO penalty parameter.

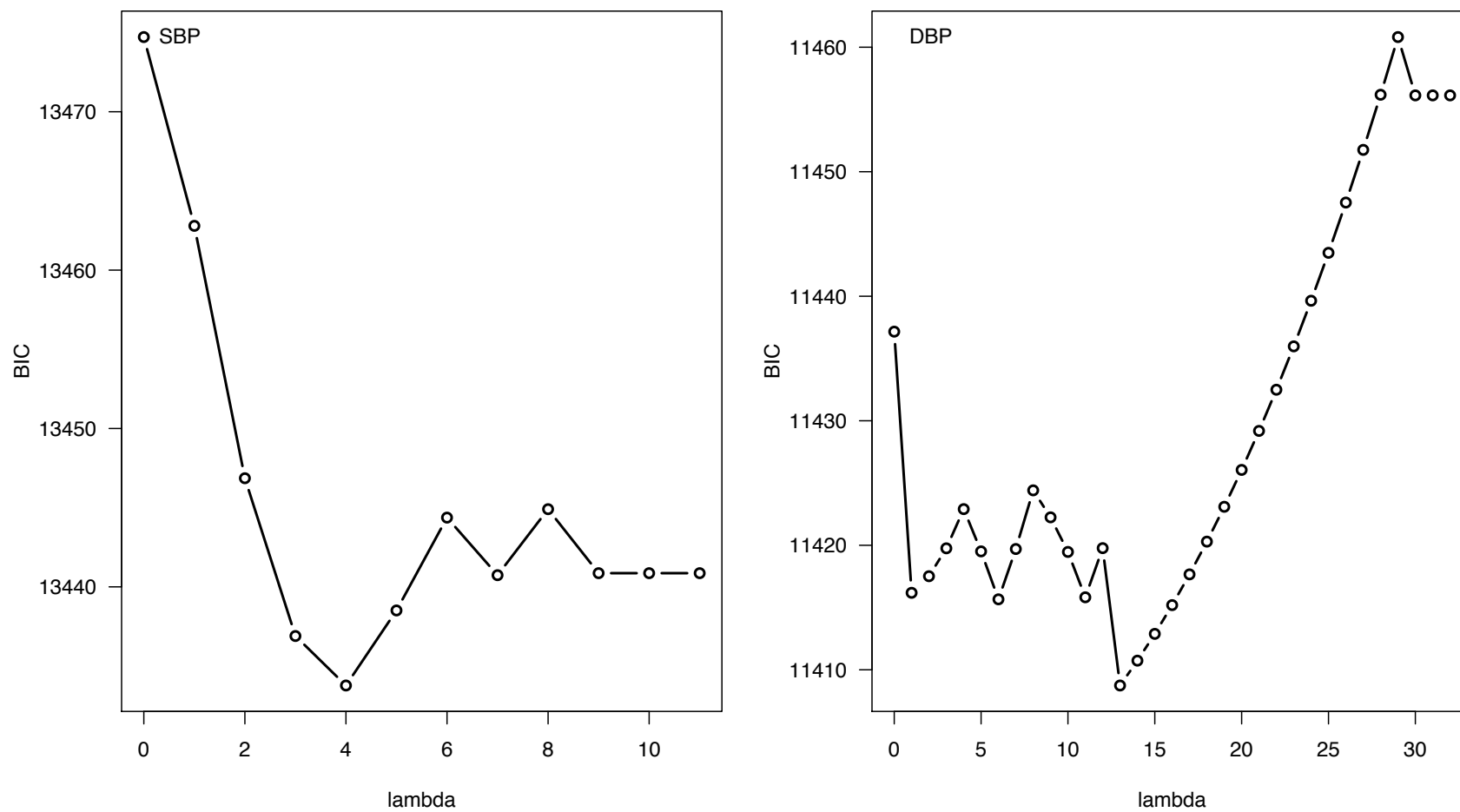**Figure 2.** LASSO coefficient paths: plot of coefficient profiles for $PM_{2.5}$ components as a function of λ.

Figure 1.

Figure 2.